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(57) Abstract

A method is proposed for detecting cancer and particularly malign tumors in a person by using the NMR spectrum of blood plasma. In a recorded spectrum the resonances are determined and for these values mathematically defineable properties are calculated such as in the simplest case the height of the resonance and the value of the width of the resonance at half height. Advantageously at least two different mathematically defineable properties are used and the corresponding values are considered as entered in a multidimensional space. In this there are defined regions of expected and not expected malignancy and if the values are located within either region the corresponding conclusion can be obtained in regard of the fact if the person has or has not cancer. If the values are located outside these regions a safe conclusion cannot be obtained. Further, as a criterion can be used the difference and/or the quotient of the values determined for some characteristic property of these resonances. As a characteristic property the peak value, the width at half height of the area can be chosen. Instead of the width at half height the value can be used which is obtained by first determining the total area of a resonance over a particular level and by dividing this area by the height of the resonance line over the underlying resonances.

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A method for the detection of malignancy

This invention is primarily concerned with a method for the detection of malignant tumors. Such tumors are the primary cause of death for some 20% of the population in for example Japan, Sweden and the United States of America. Cancer is even more important as a cause of early death; for people dying in the employed ages in Sweden some 53% of the women and 29% of the men died of cancer. An early detection of malignant tumors does improve the probability for a successful treatment. Various screening methods have been proposed to systematically screen the population in order to find malignant tumors earlier than the time when the acute symptoms will indicate their presence. One example is mammography screening. The mammography program in Sweden is recommended to involve regular X-ray screening of women between the ages of 40 and 74 with 1.5 to 2 years intervals, each exposure to be checked by two radiologists. The fulfillment of this program has been delayed, and the ambitions have been reduced mainly due to the lack of sufficient number of qualified radiology personnel. The costs of such a program is high. Other disadvantages are that very early (= small) tumors cannot be found, that some developed tumors will pass without being detected and that one third of the patients in surgery will be found not to have malignant tumors.

A method has been disclosed by Fossel in the European Patent Application with the publication number 0 234 524. According to Fossel, NMR (Nuclear Magnetic Resonance) parameters for protons of lipidmethyl and/or -methylene groups are determined and compared to the corresponding values for healthy patients. The width of the metyl and methylene groups is measured at half-height as a determination of spin-spin relaxation time which is the parameter used. The method according to Fossel has been investigated at many independent laboratories and the conclusion (The New England Journal of Medicine, April 5 1990, Vol. 322, No. 14, p. 1002) is that "the line widths described by Fossel el al. have been shown not to be significantly associated with the presence of cancer".

One purpose of the present invention is to offer a method to find tumors of different sizes including small ones (that

is, enabling early treatment), to find tumors of different types, and to do this at a low cost level not requiring large amounts of qualified personnel.

A more limited purpose of the present invention is to offer a method to make a first selection among patients, using its comparatively low cost and low requirement of individual judgement by skilled professional personnel to divide the large populations subjected to initial screening into two groups of patients, one comprising those who can be regarded as having no cancer and another group comprising those who should be subjected to further study.

A further purpose of the present invention is to offer means to divide large groups of people being screened for cancer into three groups:

those who can be regarded as having no cancer;

those for which the test can be assumed to be irrelevant, for example because they can be assumed to have eaten something that disturbs the test method or because of indications of wrong handling of the blood sample. In many cases they should be retested using the same screening method as before;

those who should be subjected to further study; the test method giving reason to belive there is a high probability that these screened persons have a malign tumor.

The main purpose therefor is to reduce the agony associated with messages from a cancer screening department that the more costly test should be performed. Most people dislike information indicating that they may have cancer.

The method according to the invention is preferrably performed by extracting a blood plasma sample from the patient, for example according to the procedures recommended by Fossel in EP-A-0 234 524. The blood may be drawn into a "Vacutainer" with EDTA or citrate as anti-coagulant. The plasma should preferably be separated within 12 hours and stored at about +4°C (it must never be frozen). A sample with visible hemolysis must be replaced by a new sample. The sample should then be analyzed within 6 days. Dideuteriumoxide should be added to the sample in a NMR tube and a spectrum should be taken using a NMR spectrometer operating at 360 MHz or higher.

The method is based upon the well founded assumption that

there is a some relation between NMR spectra of some human body tissue or fluid from a human being, for example blood serum, and the existence of a malign tumor in the same individual. The method described by Fossel seems only to touch upon one aspect of this assumed relation. An evident example of this is that the preferred embodiment of the invention according to Fossel (The New England Journal of Medicine, vol. 315, Nov. 27, 1986) is the mean value, that is an addition or a sum, of the line widths of the methyl and methylene resonances. As will be shown below, the data available to us seem to indicate that the difference between the line widths of these methyl and methylene resonances also can be used as a criterion and gives almost the same grouping or classification of the patients. Obviously, the appearently relevant information comprised in the line width differences is completely eliminated by the line width addition involved in the calculation of the mean.

In the mentioned published European application it is indicated on page 10, lines 5 - 8, that the measured or derived line widths, by some methods, are classified as normal or abnormal by means of comparison, subtraction or some other mathematical operation. In this document it is not the purpose to make a comparison of line widths for various peaks within a spectrum to each other but only of line widths to reference values. Neither it is the purpose to make a subtraction of line widths for various peaks within a spectrum by each other but only of line widths by reference values. This is obvious from the lines 2 - 5 on the same page.

According to the invention values are determined for at least two mathematically defineable properties of a spectrum of a blood plasma sample. These are then entered in a multidimensional space having at least two dimensions and then are inserted, suitably after performed tests, border lines or multidimensional border surfaces in this space in order to define regions of expected malignancy, that is when the values of a sample is located inside such a region it can be expected, with a good probility, that the person who has given the sample has a malign tumor. This multidimensional space may in the same way be divided into further regions of expected, evident non-malignancy, that is when the value of a sample is located in

these regions the test person, with a good probability, has no malign tumors. In a third set of regions the values obtained may be considered as irrelevant and a new blood plasma sample is taken from the person on a new occasion.

The border lines or the border surfaces of the various regions can be determined by a study of blood plasma samples from persons for whom the existens or nonexistence of cancer is already known. The borders or limits of the regions may then be determined in such a way that they are dependant of other variables which are easily detected and are associated with the person tested, for example age, sex, triglyceride concentration in the blood.

The values used in a spectrum and the regions chosen in the multidimensional space are advantageously chosen in such a way that the conditions actually mean a comparison of the height or the size of various resonance peaks of the spectrum, for instance that a difference or a quotient is formed, where the values for the peaks are provided with different weights. Thus generally a weighted sum can be formed of a number of values associated with different resonance peaks, where at least two of said weights have opposite signs to each other or a weighted sum of logarithms of the values, where in the same way at least two of the weights have opposite signs to each other.

The method according to the invention will now be described with reference to the accompanying drawings.

In Figure 1 is shown a typical NMR spectrum of the non-water components of a plasma sample. The marked height measurements in the Figure are used to calculate criterion 1 according to the present invention.

In Figure 2 is shown the correlation between a width measurement according to the invention. As an illustration is shown a typical NMR spectrum of the non-water components of a plasma sample. The marked heights and the area in the spectrum are used to calculate criterion 6, 7, 8 and 9 according to the present invention.

In Figure 3 is shown a diagram where the values according to criterion 1 are plotted against the values according to criterion 4.

In Figure 4 is shown a diagram where the values according

to criterion 2 are plotted against the values according to criterion 4.

In Figure 5 is shown a diagram where the values according to criterion 3 are plotted against the values according to criterion 4.

In Figure 6 is shown a diagram where the values according to criterion 2 are plotted against the values according to criterion 1.

In Figure 7 is shown a diagram where the values according to criterion 3 are plotted against the values according to criterion 1.

In Figure 8 is shown a diagram where the values according to criterion 9 are plotted against the values according to criterion 6.

Criterion 1 according to the invention is based upon the use of the peak intensities of the metylene and methyl resonances over the broad underlying resonances. The height of the methylene and methyl resonances over the broad underlying resonances are measured (see Figure 1) and the quotient between these two heights is calculated. For the sample according to Figure 1 the quotient is (82.5/29.0 =) 2.84. This quotient is then used to discriminate between two groups of patients, those who can be regarded as having no cancer and those who should be subjected to further study. Presently available data indicates that for the limited purpuse of eliminating most people from more expensive tests like x-ray mammography, a limit of 1.8 is suitable; patients above this value should be subjected to further study. In the case the method is to be used as the sole indication of malignany a value of 2.0 - 2.1 seems more appropriate. In both cases the limits apply to measurements using 360 to 400 MHz proton resonances.

Criteria 2 and 3 according to the invention are based upon the full width at half height of the methylene and methyl resonances (the same basic value as used by Fossel). In the method disclosed by Fossel in EP-A-0 234 524, the only processing performed of these half height values is the creation of composite linewidths, particularly the average of the half height values for the methylene and methyl resonances. Available data indicates that also other processing methods of

these half height values have a value as an indication of cancer.

According to criterion 2, the difference between the half height values for the methylene and methyl resonances are used as an indication of cancer. This difference is then used to discriminate between two groups of patients, those who can be regarded as having no cancer and those who should be subjected to further study. Available data indicates that for the limited purpose of eliminating most people from more expensive tests like X-ray mammography, a limit of 5.5 Hz is suitable; patients below this value being subjected to further study. In the case the method is to be used as the sole indication of malignany a value of about +4.5 Hz seems more appropriate. In both cases the limits apply to measurements using 360 to 400 MHz proton resonances.

According to criterion 3, the quotient between the half height widths for the methylene and methyl resonances is used as an indication of cancer. This quotient is then used to discriminate between two groups of patients, those who can be regarded as having no cancer and those who should be subjected to further study. Available data indicates that for the limited purpose of eliminating most people from more expensive tests like x-ray mammography, a limit of 1.2 is suitable; patients below this value should be subjected to further study. In case the method is to be used as the sole indication of malignany a value of about 1.15 seems more appropriate. In both cases the limits apply to measurements using 360 to 400 MHz proton resonances.

Criterion 4 is the full width at half height for the methylene resonance and is known in prior art.

Criterion 5 is a weighted sum (for example the simple average) value of the full width at half height for the methylene and methyl resonances, i.e. the prior art Fossel criterion. Using 360 or 400 MHz NMR systems, a mean value of 33 Hz has been used to distinguish between malign tumors (less than 33 Hz) and other.

Criterion 6 is similar to criterion 4 but is calculated in another way. One problem affecting the full width at half height for the methylene resonance is its sensitivity to minor

peaks from lactate methyl protons. This is illustrated in Figure 2. In this Figure a part of the NMR spectrum of sample 12 can be seen. According to the prior art methods, the width at half height (50%) is calculated and found to be 48.4 Hz. Obviously, a minor noise or only slightly different physical properties would have given a value of 44.2 Hz. Criterion 6 according to the invention uses the total area (shadowed in Figure 2) over a certain level (arbitrarily set as 80% of the height over the underlying resonances; other limit values are also possible). This area is then divided by the height of the peak over the underlying resonances. The diagram in Figure 2 illustrates the correlation between the criterion 6 according to the invention and the prior art criterion 4. The sample 12 is in the diagram indicated at two positions; 12W indicates the prior art value and 12N indicates the value that would have been obtained if the lactate peak would have been slightly lower.

Criterion 7 according to the invention is similar to criterion 5 but uses the area/height method according to the invention in place of the prior art half-height width.

Criterion 8 according to the invention is similar to criterion 2 but uses the area/height method according to the invention in place of the prior art half-height width. As criterion 2 uses the difference of two values of similar magnitude, it is of cource important to reduce the ambiguity illustrated by sample 12 in Figure 2.

Criterion 9 according to the invention is the quotient of the areas according to the invention of the methylene and methyl resonances calculated according to the invention. The diffuse base of the methyl resonance may require a careful selection of the area calculation limit value, and it is likely that this limit value should be different for the methylene (maybe 80%) and for the methyl (maybe 60%) peaks.

In the method according to the invention, one or more mathematical criteria, using for example the peak values like in criterion 1, some measure based on a (weighted) sum of, a quotient of or a (weighted) difference between some measure of the width like criteria 2, 3, 4, 5, 6, 7 or 8, or some other mathematically defineable property like the total area like

criterion 9, are used and are calculated for some NMR resonance lines in a NMR resonance spectrum. These calculated values might be inserted into a (multidimensional) space. In this (multidimensional) space border lines (or multidimensional border surfaces) are inserted. These border lines are obtained using values from already screened persons for whom the existence or non-existenc of malign tumors are already known. The borderlines (or the multidimensional surfaces) can be a function of age, sex, triglyceride concentration in the blood, and other variables found to be relevant.

Obviously, the peak value (i.e. the peak intensity over the broad underlying resonances) can be substituted by the intensity over the broad underlying resonances at some specified full width, and the width at half height can be substituted by the width at any other height fraction like 75% of the height over the broad underlying resonances.

The method disclosed by Fossel is a special case of this general method, using only criterion 5 and a single-dimension space, i.e. all data are put on a line.

Some examples of the method will now be given referring to the Figures. As it is extremely difficult to illustrate more than two dimensions, all Figures are limited to two dimensions. In many cases such simplifications of the more general method are likely to give most of the advantages of the general method and are undeniably much more easily illustrated. In the example illustrated, four criteria 1, 2, 3 and 4 are used. This enables 6 orthogonal projections on two-dimensional plots. Only 5 of these are shown in Figures 3 - 7.

All Figures are concerned with data for the same set of samples. Among these 22 test samples some origin from patients of a hospital, some of which have malign tumors. The samples are marked with the numbers 1 - 22. To illustrate the sensitivity of the measured values three samples from one and the same, apparently healthy, individual are included: A1 before giving blood plasma, A2 after giving plasma and A3 after an uncommon breakfast (4 eggs, 2 avocados and one litre of a product similar to yoghurt). Finally, sample 17 had some sediments in it and therefore should have been rejected.

Figure 3 shows a two-dimensional plot of the criteria 1 and

4. If criterion 1 only is to be used, the projection on the vertical axis is used. For example, sample No. 4 for the criterion 1 has the value 3.5. Two areas in the plot are indicated; they are tentative areas for expected malignancy and non-malignancy. Due to the lack of enough relevant data, the indicated borderlines are only preliminary.

Figure 4 shows a two-dimensional plot of the criteria 2 and 4. If criterion 2 only is to be used, the projection on the vertical axis is used. For example, sample 4 has the value +2 Hz for the criterion 2. Two areas in the plot are indicated; they are tentative areas for expected malignancy and non-malignancy. Due to the lack of enough relevant data, the indicated borderlines are only preliminary. Criterion 2 is the direct opposite of the Fossel preferred criterion, that is the difference is used instead of the sum or the average.

Figure 5 shows a two-dimensional plot of the criteria 3 and 4. If criterion 3 only is to be used, the projection on the vertical axis is used. For example, sample 4 has the value 1.11 for the criterion 3. Two areas in the plot are indicated; they are tentative areas for expected malignancy and non-malignancy. Due to the lack of enough relevant data, the indicated borderlines are extremely preliminary.

Figure 6 shows a two-dimensional plot of the criteria 2 and 1. Two areas in the plot are indicated; they are tentative areas for expected malignancy and non-malignancy. Due to the lack of enough relevant data, the indicated borderlines are only preliminary.

Figure 7 shows a two-dimensional plot of the criteria 3 and 1. Two areas in the plot are indicated; they are tentative areas for expected malignancy and non-malignancy. Due to the lack of enough relevant data, the indicated borderlines are only preliminary.

As can be seen, most samples on all plots are located along a line or in a band that is rather narrow. This band is broken in the middle to form two areas. Most samples group themselves neatly into these two areas. There are two main groups:

The "malign" group consists of samples Nos. 1, 5, 8, 11, 13, 14, 20 and 22. With the possible exeption of No. 22 (33.7 Hz) they are all malign according to the 33 Hz limit in the

Fossel criterion.

The "non-malign" group consists of samples 3, 6, 7, 9, 10, 12, 18, 19 and 21. They are all non-malign according to the 33 Hz limit in the Fossel criterion.

Sample No. 17 had some sediments. In all plots but one it is located on the border of the non-malign area facing the malign area, but also in the last one (Figure 3) it is close to that end. It is non-malign according to the 33 Hz limit in the Fossel criterion (37.7 Hz).

Four samples having Nos. 2, 4, 15 and 16 are on most plots far away from the other groups.

In all plots, the samples Nos. 2 and 4 are closer to the malign group and No. 2 is closest. Both are very much on the malign side according to Fossel (No. 2 with 25 Hz and No. 4 with 19 Hz).

Sample No. 16 is interesting. It is clearly on the non-malign side using the Fossel 33 Hz limit (36.6 Hz; four of the 9 samples in the "non-malign" group above have lower Fossel values). In three plots it is however closer to the malign area.

Sample No. 15 is similar. It is located on the non-malign side using the Fossel 33 Hz limit (35.8 Hz; two of the 9 samples in the "non-malign" group above have lower Fossel values and one is very close, having 36.0 Hz). In two of the plots it is however in the very center of the malign area and in two it is very close.

Samples A1 - A3 is taken from the same individual but A2 is taken after a plasma donor tap and A3 after an uncommon breakfast. The Fossel readings are a "healthy" 38.3 Hz for A1 but a marginal 34.7 Hz for A2 and an alarming 23.4 Hz for A3. 23.4 Hz is lower (that is, more "malign") than all the eight samples in the "malign" group above. Only sample No. 4 has a lower Fossel reading.

One of the purposes of the present invention is to reduce the unnecessary agony likely to occur if someone after a routine cancer screening will obtain a false positive indication. Using the Fossel criterion only, this would have happened to A3. In the diagrams in Figures 3 - 7 it is however evident that A3 is far away from the "malign" areas even if it

is close in some diagrams.

Much more data are required to set well founded borders for the "malign" and "non-malign" areas above.

In Figure 8 a plot using two other criteria (6 and 9) is shown. The limit values for criterion 9 requires much more data in order to be used, but also here the "malign" and "non-malign" samples are clustered together (with the exception of sample No. 19 unless the dotted borderline is used). Sample No. 16 is close to the malign area (or within it if the dotted borderline is used) and samples Nos. 2 and 4 are farther away but still closer to the malign side.

Claims

1. A method of detecting cancer, particularly tumors, comprising the following steps:

taking a blood plasma sample of a person,

recording a NMR spectrum of the blood plasma sample,

determination of values of mathematically defineable properties of resonances in the NMR spectrum,

characterized in

that for the blood sample the values are determined for at least two different mathematically defineable properties,

that these values for the sample are inserted in a multidimensional space thus having at least two dimensions,

that border lines or multidimensional surfaces are inserted in the multidimensional space in order to define regions of expected malignancy,

that it is determined if the values for the sample are located within the border lines or the multidimensional surfaces and that in this case the person is supposed to have cancer.

2. A method according to claim 1,

characterized in

that border lines or multidimension surfaces are inserted in the multidimensional space to limit regions of expected non-malignancy,

that it is determined if the values for the sample are located within these border lines or these multidimensional surfaces and that in this case the person is supposed not to have cancer.

3. A method according to claim 2,

characterized in

that if the values for a sample are located outside the border lines or the multidimensional surfaces, which define regions of expected malignancy and non-malignancy, the values are considered as irrelevant and the person is tested again, for example by repeating the method with a new blood sample.

4. A method of detecting cancer, particularly tumors, comprising the following steps:

obtaining a blood plasma sample of a person,

recording a NMR spectrum of the blood plasma sample,

determination of values of mathematically defineable properties of resonances in the NMR spectrum,

characterized in

that for the blood sample the values are determined for at least two different mathematically defineable properties,

that these values for the sample are inserted in a multidimensional space thus having at least two dimensions,

that border lines or multidimensional surfaces are inserted in the multidimensional space in order to define regions of expected non-malignancy,

that it is determined if the values for the sample are located within the border lines or the multidimensional surfaces and that in this case the person is supposed not to have cancer.

5. A method according to one of the preceding claims, characterized in

that the border lines or the multidimensional surfaces are obtained from data for already examined persons for whom the existence or non-existence of cancer is previously known.

6. A method according to one of the preceding claims, characterized in

that the border lines or the multidimensional surfaces are a function of variables associated with the person such as age, sex, triglyceride concentration in the blood.

7. A method according to one of the preceding claims, characterized in

that the mathematically defineable properties comprise

characteristic properties of the resonances such as

a measure of the width of a resonance, for example

the width of a resonance at some level of the height of the resonance over the underlying resonances, such as

the width at half height of the resonance,

the value which is obtained

by first determining the total area of a resonance over a particular level of the height over the underlying resonances,

by then dividing this area by the height of the resonance over the underlying

resonances,
the height of a resonance over the underlying resonances or generally the intensity of a resonance over the broad underlying resonances at some specified full width,
the area of a resonance, and/or
the values which are obtained by forming the sum or a weighted sum of
a measure of the width of a resonance, for example
the width of a resonance at some level of the height of the resonance over the underlying resonances, such as
the width at half height of the resonance,
the value which is obtained
by first determining the total area of a resonance over a particular level of the height over the underlying resonances,
by then dividing this area by the height of the resonance over the underlying resonances,
the height of a resonance over the underlying resonances or generally the intensity of a resonance over the broad underlying resonances at some specified full width,
the area of a resonance, and/or
the values which are obtained by forming the difference and/or a weighted difference of
a measure of the width of a resonance, for example
the width of a resonance at some level of the height of the resonance over the underlying resonances, such as
the width at half height of the resonance,
the value which is obtained
by first determining the total area of a resonance over a particular level of the height over the underlying resonances,
by then dividing this area by the height of the resonance over the underlying resonances,

the height of a resonance over the underlying resonances or generally the intensity of a resonance over the broad underlying resonances at some specified full width,
the area of a resonance, and/or
the values which are obtained by forming a quotient of
a measure of the width of a resonance, for example
the width of a resonance at some level of the height of the resonance over the underlying resonances, such as
the width at half height of the resonance,
the value which is obtained
by first determining the total area of a resonance over a particular level of the height over the underlying resonances,
by then dividing this area by the height of the resonance over the underlying resonances,
the height of a resonance over the underlying resonances or generally the intensity of a resonance over the broad underlying resonances at some specified full width,
the area of a resonance.

8. A method of detecting cancer, particularly tumors, comprising the following steps:
obtaining a blood plasma sample of a person,
recording a NMR spectrum of the blood plasma sample,
determination of a characteristic property of resonances in the NMR spectrum,
using the determined values to determine if cancer is present,
characterized in
that the difference or a weighted difference of the determined values is formed,
that this difference is compared to predetermined reference values and
that from the result of the comparison it is determined if cancer is present.

9. A method according to claim 8,

characterized in

that the characteristic property is the width of the resonance at some level of the height of the resonance over the underlying resonances, such as the width of the resonance at half height.

10. A method according to claim 8,

characterized in

that the characteristic property is obtained

by first determining the total area of a resonance over a particular level of the height over the underlying resonances,

by then dividing this area by the height of the resonance over the underlying resonances.

11. A method of detecting cancer, particularly tumors, comprising the following steps:

obtaining a blood plasma sample of a person,

recording a NMR spectrum of the blood plasma sample,

determination of a characteristic property of resonances in the NMR spectrum,

using the determined values to determine if cancer is present,

characterized in

that the quotient of the determined values is formed,

that this quotient is compared to predetermined reference values and

that from the result of the comparison it is determined if cancer is present.

12. A method according to claim 11,

characterized in

that the characteristic property is the the height of the peak of the resonance over the underlying resonances or generally the intensity of a resonance over the broad underlying resonances at some specified full width.

13. A method according to claim 11,

characterized in

that the characteristic property is the area of the resonance.

14. A method according to claim 11,

characterized in

that the characteristic property is the width of the resonance at some level of the height of the resonance over the underlying resonances, such as the width of the resonance at half height.

15. A method according to claim 11, characterized in that the characteristic property is obtained by first determining the total area of a resonance over a particular level of the height over the underlying resonances, by then dividing this area by the height of the resonance over the underlying resonances.

16. A method of detecting cancer, particularly tumors, comprising the following steps:
obtaining a blood plasma sample of a person,
recording a NMR spectrum of the blood plasma sample,
determination of a characteristic property of resonances in the NMR spectrum,
using the determined values to determine if cancer is present,
characterized in
that the characteristic property is the width of the resonance at some level of the height of the resonance over the underlying resonances, such as the width at half height of the resonance, and/or
that the characteristic property is obtained by first determining the total area of a resonance over a particular level of the height over the underlying resonances and by then dividing this area by the height of the resonance over the underlying resonances.

17. A method according to claim 16, characterized in that for the determination if cancer is present the quotient of the determined values is formed, that this quotient is compared to predetermined reference values and that from the result of the comparison it is determined if cancer is present.

18. A method according to claim 16,
characterized in
that for the determination if cancer is present the sum or a weighted mean of the determined values is formed,
that this sum or mean is compared to predetermined reference values and
that from the result of the comparison it is determined if cancer is present.

19. A method according to claim 16,
characterized in
that for the determination if cancer is present the difference or a weighted difference of the determined values is formed and
that this difference is compared to predetermined reference values and
that from the result of the comparison it is determined if cancer is present.

Figure 1

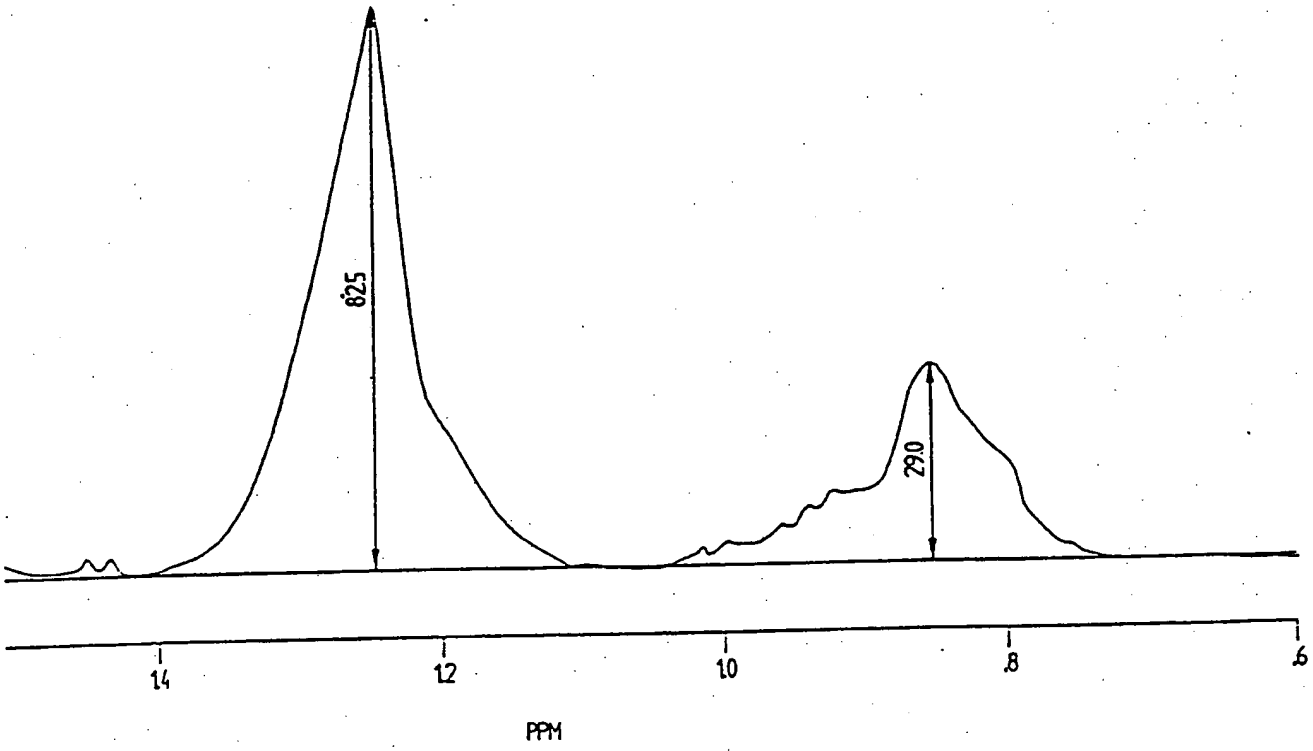


Figure 2

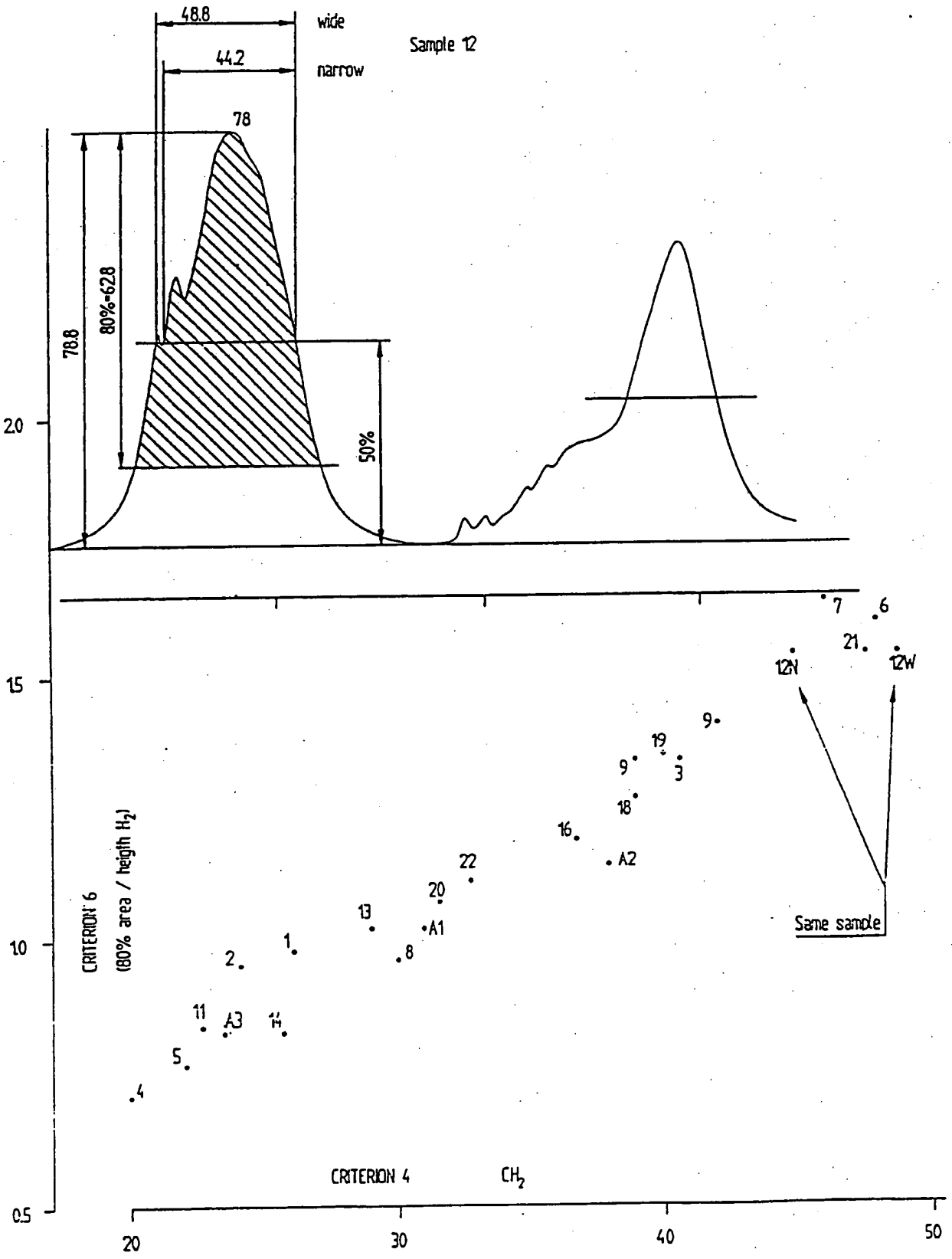

48.8
wide
44.2
narrow
Sample 12
78
78.8
80%-62.8
50%
2.0
1.5
1.0
0.5
CRITERION 6
(80% area / height H_2)
CRITERION 4
CH_2
20
30
40
50
7
6
21
12N
12W
9
19
3
9
18
16
A2
22
20
13
A1
1
2
8
11
A3
14
5
4
Same sample

Figure 3

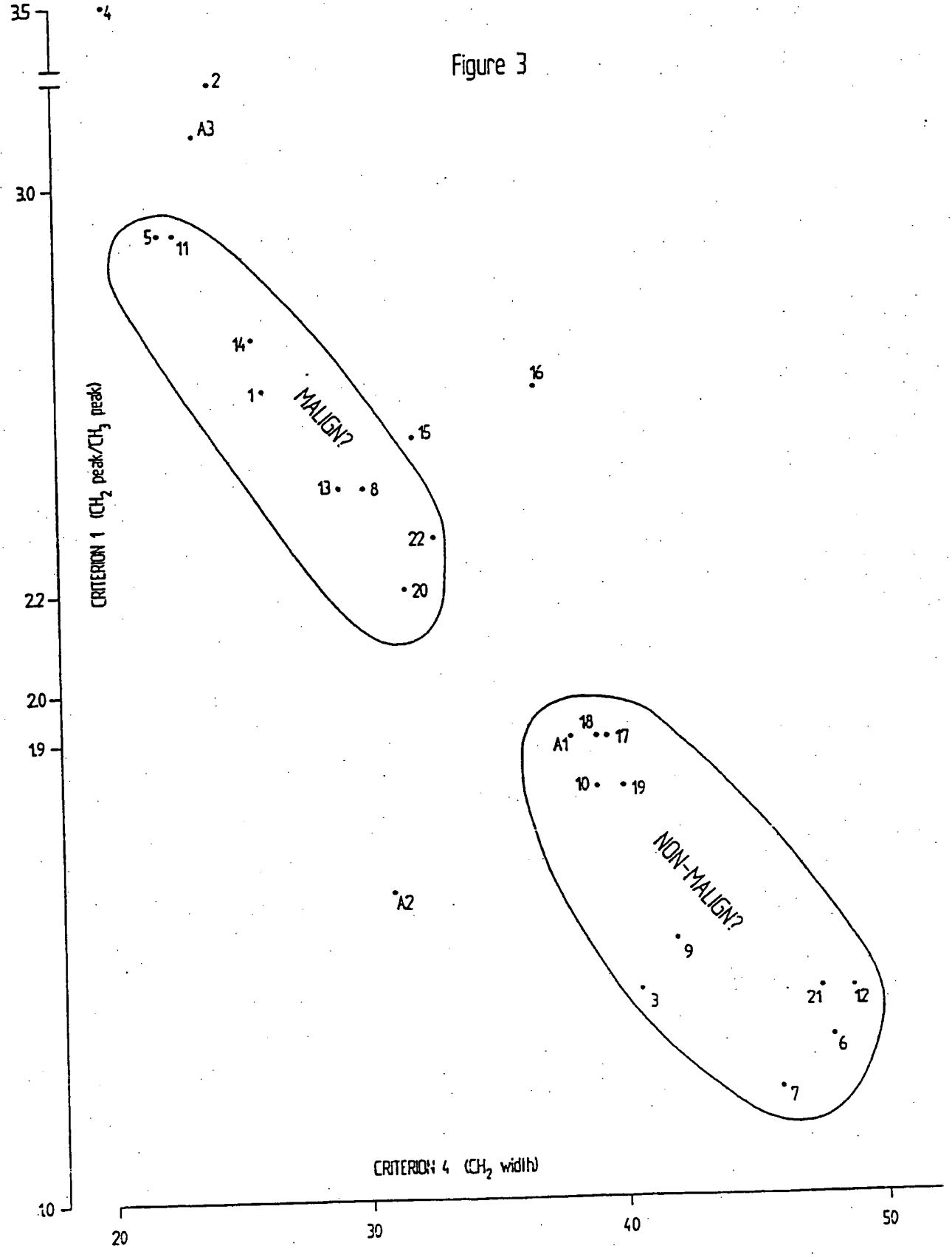

35
30
22
20
19
10
CRITERION 1 (CH_2 peak/CH_3 peak)
MALIGN?
NON-MALIGN?
A1
A2
A3
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
20
30
40
50
CRITERION 4 (CH_2 width)

Figure 4

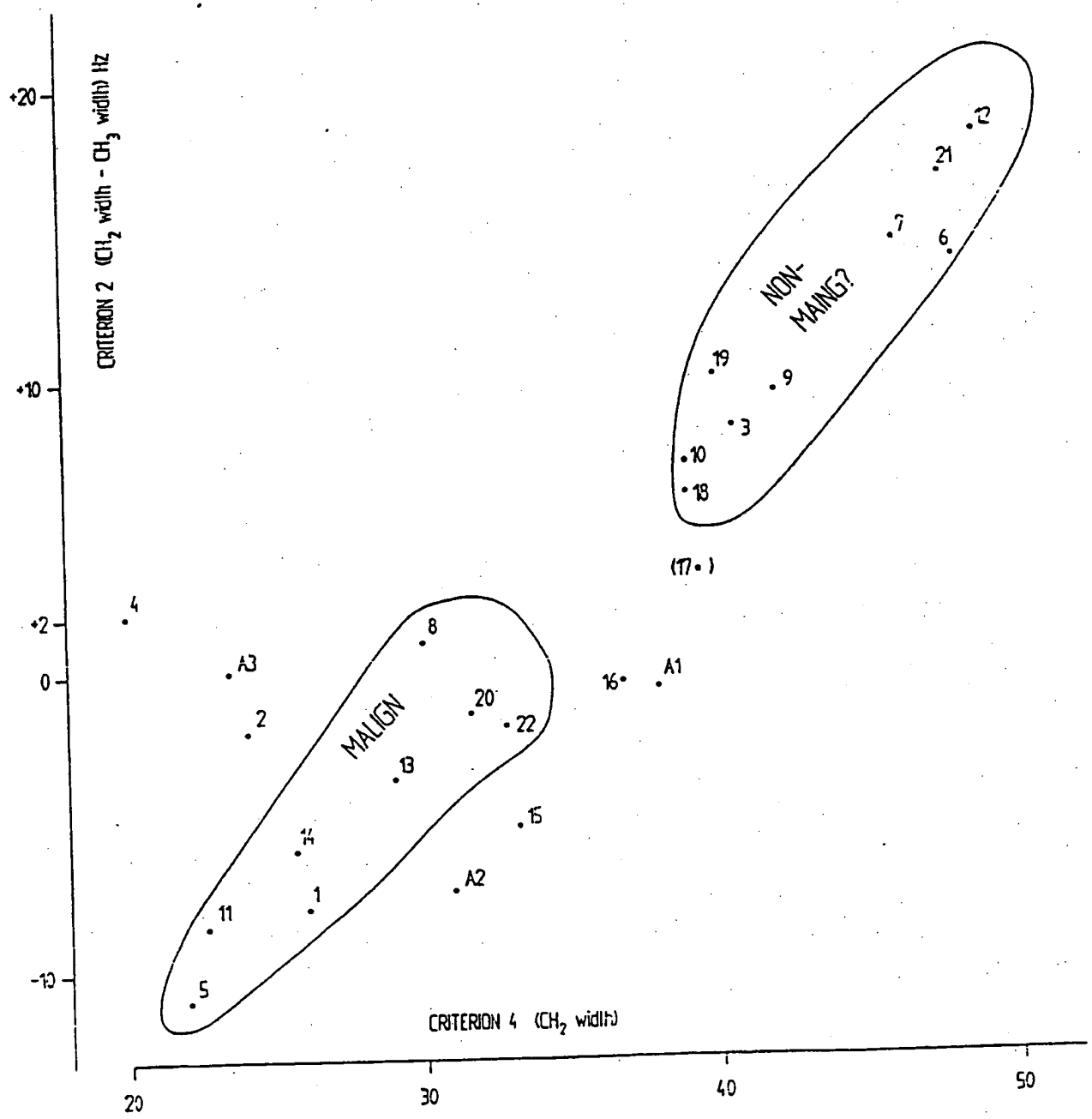

CRITERION 2 (CH_2 width - CH_3 width) Hz
+20
+10
+2
0
-10
CRITERION 4 (CH_2 width)
20
30
40
50
MALIGN
NON-MAING?
(17)
A1
A2
A3
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
18
19
20
21
22

Figure 5

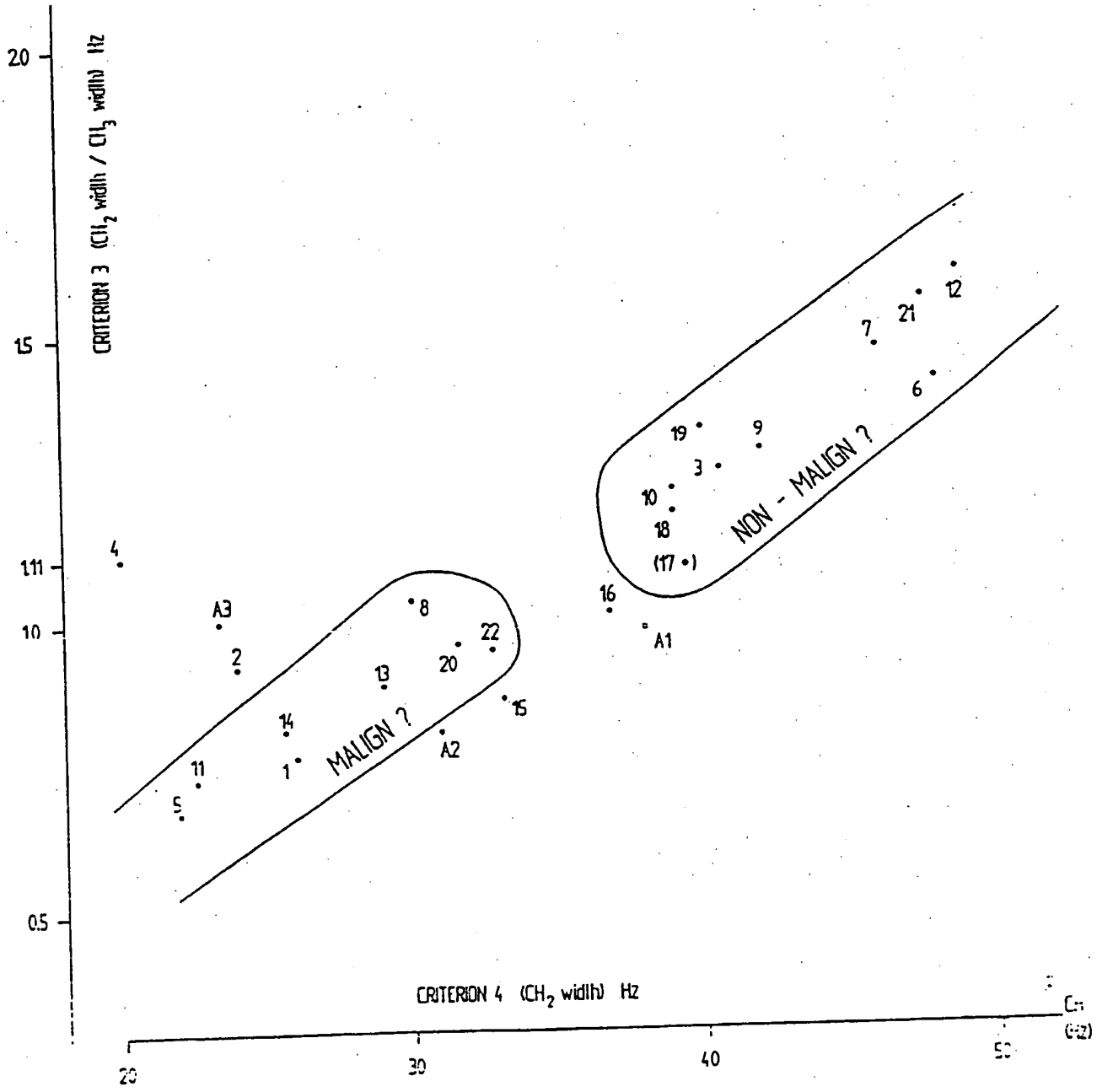

CRITERION 3 (CH_2 width / CH_3 width) Hz
20
15
1.11
1.0
0.5
CRITERION 4 (CH_2 width) Hz
20
30
40
50
MALIGN ?
NON - MALIGN ?
A1
A2
A3
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
18
19
20
21
22
(17 •)

Figure 6

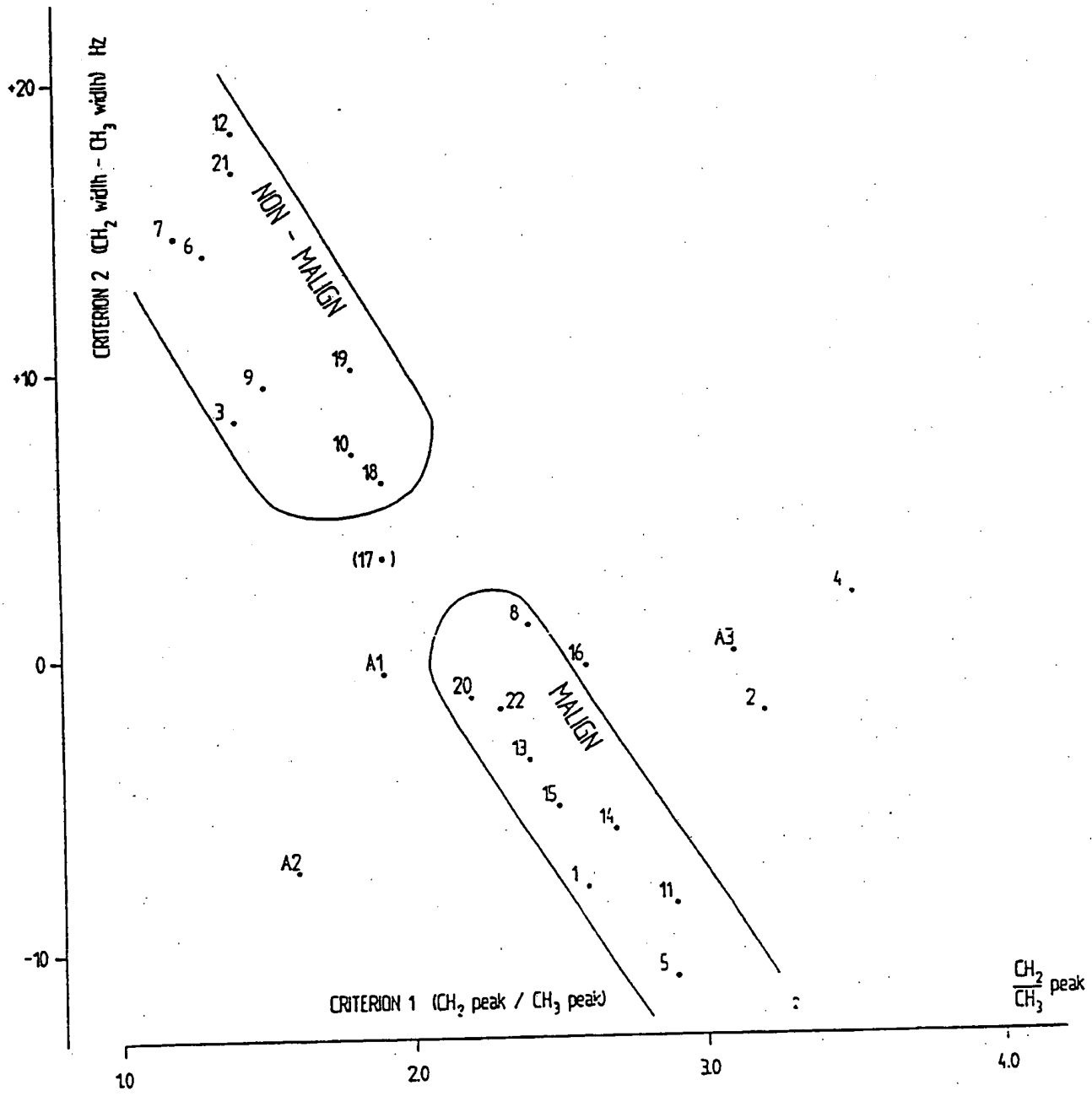

+20
+10
0
-10
CRITERION 2 (CH_2 width - CH_3 width) Hz
NON - MALIGN
MALIGN
12
21
7
6
19
9
3
10
18
(17 •)
4
8
16
A3
A1
20
22
2
13
15
14
1
11
A2
5
CRITERION 1 (CH_2 peak / CH_3 peak)
$\frac{CH_2}{CH_3}$ peak
1.0
2.0
3.0
4.0

Figure 7

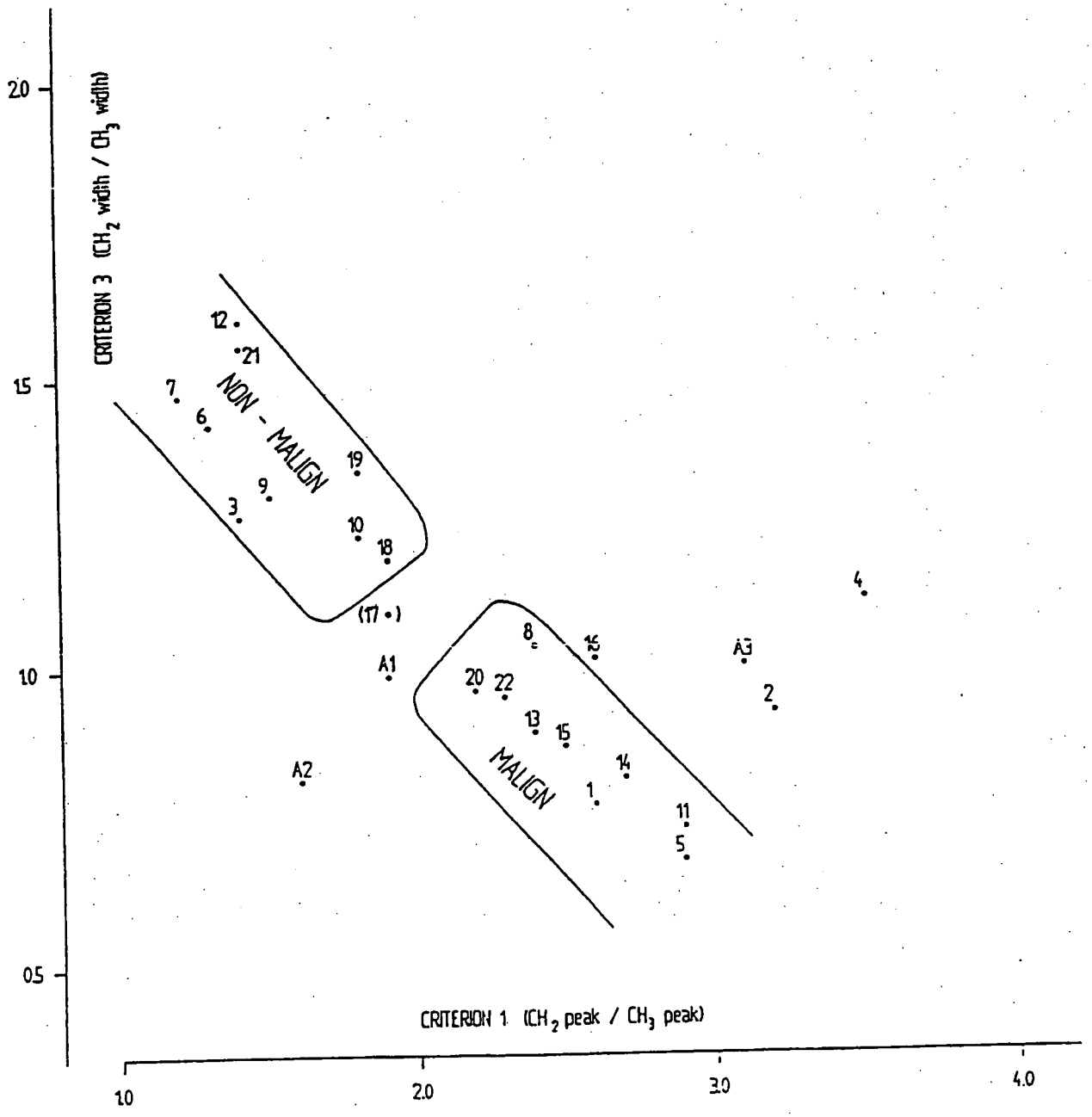
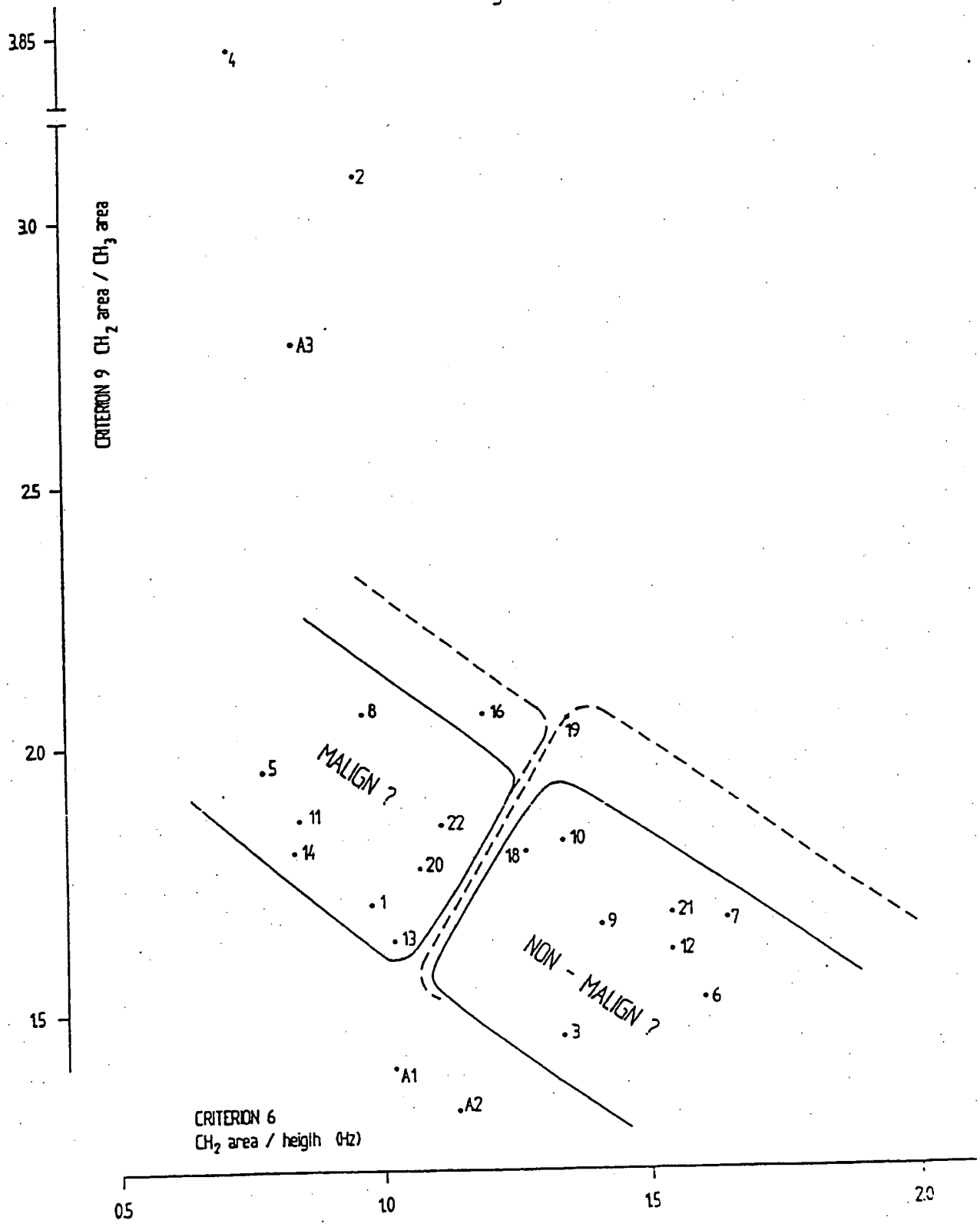

CRITERION 3 (CH_2 width / CH_3 width)
2.0
1.5
1.0
0.5
NON - MALIGN
MALIGN
12
21
7
6
19
9
3
10
18
(17)
8
16
A3
4
A1
20
22
2
13
15
14
A2
1
11
5
CRITERION 1 (CH_2 peak / CH_3 peak)
1.0
2.0
3.0
4.0

Figure 8


3.85
3.0
2.5
2.0
1.5
CRITERION 9 CH_2 area / CH_3 area
4
2
A3
8
16
19
5
MALIGN ?
11
22
14
20
18
10
1
9
21
7
13
12
NON - MALIGN ?
6
3
A1
A2
CRITERION 6
CH_2 area / heigth (Hz)
0.5
1.0
1.5
2.0

INTERNATIONAL SEARCH REPORT

International Application No PCT/SE 91/00338

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC5: A 61 B 5/055, G 01 N 24/08, G 01 R 33/46

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
IPC5	A 61 B; G 01 N; G 01 R

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in Fields Searched[8]

SE,DK,FI,NO classes as above

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category *	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	EP, A3, 0234524 (THE BETH ISRAEL HOSPITAL ASSOCIATION) 2 September 1987, see page 9, line 51 - line 56; page 10, line 1 - line 8 --	16
A	EP, A1, 0361214 (OTVOS, JAMES D.) 4 April 1990, see the whole document --	1-19

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* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
1st August 1991	1991 -08- 05
International Searching Authority	**Signature of Authorized Officer**
SWEDISH PATENT OFFICE	UDO HINZ

Form PCT/ISA/210 (second sheet) (January 1985)

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.PCT/SE 91/00338

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the Swedish Patent Office EDP file on 91-06-27
The Swedish Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A3- 0234524	87-09-02	AU-B-	600931	90-08-30
		AU-D-	6918987	87-08-27
		JP-A-	62276459	87-12-01
		US-A-	4912050	90-03-27
		US-A-	4918021	90-04-17
EP-A1- 0361214	90-04-04	JP-A-	2116743	90-05-01
		US-A-	4933844	90-06-12